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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	**PAPER NUMBER**
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/008,355	TRAVIS ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2003*.

2a)☒ This action is **FINAL.** 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-56,58-73,75 and 77* is/are rejected.

7)☒ Claim(s) *57, 74, and 76* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1003*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response, received October 27, 2003, to the Office Action of July 25, 2003 on the Merits of this case is acknowledged. It is acknowledged that applicants have cancelled Claims 1-53 and added new Claims 54-77, which are encompassed by the elected invention. Claims 54-77 are hereby considered on their merits.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 58 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 58 is unnecessarily confusing in reciting nucleic acid molecules that hybridize to SEQ ID NO: 1 under high stringency conditions and encode a polypeptide having at least 40% identity with SEQ ID NO: 2. The hybridization conditions recited would isolate only those nucleic acid molecules having at least 95% identity with SEQ ID NO: 1; i.e., changes in about 107 nucleotides. If every said nucleotide change caused an amino acid mutation in the encoded protein, the encoded protein would have no less than 85% identity (605/712) with SEQ ID NO: 2. Therefore, Claim 58 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as their invention. For purposes of examination, the phrase "where the protein encoded by the nucleic acid has a percentage amino acid identity of greater than 40% with SEQ ID NO: 2" is rendered moot.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In the Action of July 25, 2003, Claims 39 and 41-50 were rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. Said rejection is withdrawn because Claims 39 and 41-50 have been cancelled. However, new Claims 60-73 and 75 are hereby rejected for the same reason described in the prior action.

Although the specification is enabling for the dipeptidypeptidase encoded by SEQ ID NO: 1 and set forth by SEQ ID NO: 2, the specification does not reasonably provide enablement for any nucleic acid molecule encoding any protein with dipeptidylpeptidase amidolytic activity, as recited in Claims 60-73 and 75. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 60 is so broad as to encompass any nucleic acid molecule encoding a polypeptide having dipeptidylpeptidase amidolytic activity wherein said polypeptide comprises residues 543-712 of SEQ ID NO: 2. Claim 61 is so broad as to encompass any nucleic acid molecule encoding a polypeptide having dipeptidylpeptidase amidolytic activity wherein said polypeptide comprises residues 540-712 of SEQ ID NO: 2. Claim 62 is so broad as to encompass any nucleic acid molecule encoding a polypeptide having dipeptidylpeptidase amidolytic activity wherein said polypeptide comprises residues 522-712 of SEQ ID NO: 2. Claims 63, 66, 67, 68, 69, and 70 are so broad as to encompass any nucleic acid molecule encoding a polypeptide having dipeptidylpeptidase amidolytic activity wherein said polypeptide comprises the motif

TGGNSGSPVF and wherein, when said motif is in register with residues 644-653 of SEQ ID NO: 2, the encoded polypeptide has greater than 40%, 50% 60%, 70%, 80%, and 90% identity, respectively, with SEQ ID NO: 2. Claims 71-73 are so broad as to encompass any nucleic acid molecule having at least 70%, 80%, and 90% identity, respectively, with SEQ ID NO: 1, wherein said nucleic acid molecule encodes a polypeptide having dipeptidylpeptidase amidolytic activity. Claim 75 is so broad as to encompass any nucleic acid molecule having at least 70% identity with SEQ ID NO: 1 wherein said nucleic acid molecules encodes a polypeptide having dipeptidylpeptidase amidolytic activity and having greater than 40% identity with SEQ ID NO: 2. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired dipeptidylpeptidase amidolytic activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of SEQ ID NO 2 and the nucleotide sequence of SEQ ID NO 1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any

protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of (i) Claim 60, which encompasses any nucleic acid molecule encoding a polypeptide having dipeptidylpeptidase amidolytic activity wherein said polypeptide comprises residues 543-712 of SEQ ID NO: 2; (ii) Claim 61, which encompasses any nucleic acid molecule encoding a polypeptide having dipeptidylpeptidase amidolytic activity wherein said polypeptide comprises residues 540-712 of SEQ ID NO: 2 (iii) Claim 62, which encompasses any nucleic acid molecule encoding a polypeptide having dipeptidylpeptidase amidolytic activity wherein said polypeptide comprises residues 522-712 of SEQ ID NO: 2; (iv) Claims 63, 66, 67, 69, and 70, which encompass any nucleic acid molecule encoding a polypeptide having dipeptidylpeptidase amidolytic activity wherein said polypeptide comprises the motif TGGNSGSPVF and wherein, when said motif is in register with residues 644-653 of SEQ ID NO: 2, the encoded polypeptide has greater than 40%, 50% 60%, 70%, 80%, and 90% identity, respectively, with SEQ ID NO: 2; (v) Claims 71-73, which encompass any nucleic acid molecule having at least 70%, 80%, and 90% identity, respectively, with SEQ ID NO: 1, wherein said nucleic acid molecule encodes a polypeptide having dipeptidylpeptidase amidolytic activity; or (vi) Claim 75, which encompasses any nucleic acid molecule having at least 70% identiy with SEQ ID NO: 1 wherein said nucleic acid molecules encodes a polypeptide having dipeptidylpeptidase amidolytic activity and having greater than 40% identity with SEQ ID NO: 2. The specification does not support the broad scope of Claims 60-73 and 75 because the specification does not establish: (A) regions of the protein's structure which may be modified

without effecting the dipeptidylpeptidase amidolytic activity; (B) the general tolerance of the dipeptidylpeptidase amidolytic activity to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of nucleic acid molecules encoding proteins with dipeptidylpeptidase activity having an enormous number of amino acid modifications of the dipeptidylpeptidase of SEQ ID NO: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 64 and 65, as dependent on claim 63, are rejected for the same reasons.

After providing quotes from the M.P.E.P. 2164.04, 2164.01(b), 2164.02, and 2164.03, Applicants provide the following arguments to support their request that rejection under 35 U.S.C. 112, first paragraph for lack of enablement be withdrawn.

"The specification clearly describes methods of making the claimed isolated nucleic acids (e.g. page 9, line 22 to page 12, line 26; and page 15, line 2 to page 20, line 25). Although not required, and as admitted by the Examiner, Applicants have even provided working examples of

the claimed isolated nucleic acids (e.g. pages 24-27). Further, the specification provides methods of using the claimed isolated nucleic acids (e.g., page 20, line 26 to page 23, line 20). Notably, the Examiner has not provided any reason to doubt the objective truth of the disclosure provided in the specification.

In spite of the disclosure provided in the specification as noted above, the Examiner asserted that "the specification does not reasonably provide enablement for "any nucleic acid molecule encoding any dipeptidylpepidase amidolytic activity (page 5, 6 first full paragraph of the Office Action mailed July 25, 2003). Applicants are not claiming "any nucleic acid molecule encoding any dipeptidylpepidase amidolytic activity."

Independent claims 54, 60, 63, and 71 claim isolated nucleic acids by reciting physical and/or chemical properties including, for example, hybridization conditions (e.g. independent claim 54), specific sequences (e.g., independent claim 60), and/or structural identity (e.g. independent claims 63 and 71), as further described herein below under the remarks to the rejection based on lack of written description. Independent claims 54, 60, 63, and 71 claim isolated nucleic acids by further reciting function (e.g., encoding a "protein [and variants thereof having] dipeptidylpepidase amidolytic activity").

Further, Applicants respectfully reiterate that, as quoted from the M.P.E.P. herein above, a disclosure of every operable species is not required. Applicants respectfully submit that one of skill in the art using the disclosure provided in the specification (including the working examples), would be able to make and use the entire scope of the invention as recited in, for example, independent claims 54, 60, 63, and 71. For example, the specification provides guidance to one of skill in the art in selecting amino acids for substitution into the encoded

peptidase (e.g., page 13, line 31 to page 14, line 10). Further, Applicants respectfully submit that one of skill in the art, in view of the present specification, would be enabled to select appropriate amino acids in the peptidase as candidates for substitution (e.g. page 14, line 11 to page 15, line 2).

Moreover, the specification provides one of skill in the all exemplary methods of assaying isolated nucleic acids for amidolytic activity (e.g., page 12. line 27 to page 13, line 25; page 25, line 22 to page 26, line 29 and page 26, lines 23-32)."

These arguments are not found to be persuasive for the following reasons.

Reply: The following is acknowledged. That molecular cloning, mutagenesis, and enzymatic testing of expressed proteins are common in the art. That the specification at page 9, line 22 to page 12, line 26 enables a person of skill in the art, to make and/or use the invention of any polynucleotide encoding the protein set forth by SEQ ID NO: 2. That the specification at page 15, line 2 to page 20, line 25 enables a person of skill in the art, to isolate, from a cellular or tissue source, a native protein having dipeptidylpepidase amidolytic activity and isolate, by hybridization, polynucleotides homologous to SEQ ID NO: 1. That, Applicants have disclosed which amino acid substitutions they consider to be conservative and are not claiming any nucleic acid molecule encoding any type of dipeptidlypeptidase amidolytic activity. That, Claims 60 recites residues 543-712 of SEQ ID NO: 2, that Claim 63 recites the motif TGGNSGSPVF wherein, when said motif is in register with residues 644-653 of SEQ ID NO: 2 and the encoded polypeptide has greater than 40%, and that Claim 71 recites 70% identity with SEQ ID NO: 1.

However, the specification provides insufficient guidance to enable one of skill in the art to determine which of the essentially infinite possible choices of polynucleotides encompassed

by the instant claims is likely to be successful in the desired utility. The effect of replacement of any amino acid residue in a protein can be unpredictable. Wishart et al, 1995 teach that a single mutation of a Gly residue to a Cys residue ($G^{120}C$) converts a phosphotyrosine binding-domain into a dual-specificity phosphatase (Fig 4). While, as taught by Witkowski et al, 1999, a single mutation of a Cys residue for a Gln residue ($C^{161}Q$) converts a β-ketoacyl synthase to a malonyl decarboxylase (Fig 3). Thus, the effects of even a single mutation on a protein's activity and function are unpredictable. The specification and the current state of the art fail to provide sufficient guidance to enable a person of ordinary skill in the art to make and use the scope of recited nucleic acid molecules without modifying any polynucleotide encoding SEQ ID NO: 2, or an active variant thereof, and testing the effect of the modification on the desired utility.

While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. Although mutagenesis and enzymatic testing standard in the art, the amount of mutagenesis and enzymatic testing necessary to enable one of skill in the art to determine which, of the essentially unlimited number of recited polynucleotides, have the desired utility would clearly constitute **undue** experimentation.

For these reasons, and those state above, rejection of Claims 60-73 and 75 under 35 U.S.C. 112, first paragraph for lack of enablement is maintained.

In the Action of July 25, 2003, Claims 39 and 41-50 were rejected under 35 U.S.C. 112, first paragraph for insufficient written description. Said rejection is withdrawn, because Claims 39 and 41-50 have been cancelled. However, new Claims 60-73 and 75 are hereby rejected for

the same reason described in the prior action. Claims 60-73 and 75 are rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 60-73 and 75 are directed to a large genus of DNA molecules encoding any protein having dipeptidylpeptidase amidolytic activity wherein said genus is comprised of a large number of variants of SEQ ID NO: 1 or encode a large number of variants of SEQ ID NO: 2. Said genus of DNA molecules includes any nucleic acid molecule encoding a protein having dipeptidylpeptidase amidolytic activity, wherein the polypeptides comprises (i) residues 543-712 of SEQ ID NO: 2; (ii) residues 540-712 of SEQ ID NO: 2; (iii) residues 522-712 of SEQ ID NO: 2; (iv) the motif TGGNSGSPVF and wherein, when said motif is in register with residues 644-653 of SEQ ID NO: 2, the encoded polypeptide has greater than 40%, 50% 60%, 70%, 80%, or 90% identity with SEQ ID NO: 2. Said genus of DNA molecules also includes any nucleic acid molecule encoding a protein having dipeptidylpeptidase amidolytic activity, wherein the nucleic acid molecules has at least 70%, 80%, or 90% identity with SEQ ID NO: 1 and any nucleic acid molecule having at least 70% identity with SEQ ID NO: 1, wherein said nucleic acid molecule encodes a polypeptide having greater than 40% identity with SEQ ID NO: 2. The specification teaches the structure of only a single representative species of such DNAs, SEQ ID NO: 1. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than providing a list of conservative amino acid substitutions for each of hydrophobic, polar, basic, and acidic residues (p 13) and teaching that, preferably, the dipetidylpeptidase includes the sequence TGGNSGSPV or, more preferably, TGGNSGSPVF

and that the catalytic domain of the dipetidylpeptidases preferably consist of residues 543-712 of the protein set forth by SEQ ID NO: 2, more preferably consist of residues 540-712 of the protein set forth by SEQ ID NO: 2, or most preferably consist of residues 522-712 of the protein set forth by SEQ ID NO: 2. These recited structural features do not constitute a substantial portion of the genus, as the remainder of the structure of any polypeptide with dipeptidylpeptidase amidolytic activity to be encoded by the genus of DNA molecules is completely undefined. In other words, the genus of recited DNA molecules is a large and variable genus, which has the potential to encode proteins with a large variety of activities, or no activity. Those nucleic acid molecules encoding proteins with the desired activity would constitute a small portion of the total genus. Given the lack of description of representative species having the desired activity, as encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Applicants provide the following arguments to support their request that rejection under 35 U.S.C. 112, first paragraph for insufficient written description be withdrawn.

"The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or

disclosed correlations between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. . . . There may be situations where one species adequately supports a genus.

Without more, the disclosure of one species (e.g., SEQ NO: 1 or SEQ ID NO: 2), arguably may not support a genus of nucleic acids or proteins. However, the present claims provide more than the bare sequence of one nucleic acid or one protein. Applicants respectfully submit that the present claims satisfy the written description requirement of 35 U.S.C. 112, first paragraph, for at least the reasons discussed herein below.

CLAIMS ... 63, 65, AND 66-75 RECITE BOTH FUCTIONAL AND STRUCTURAL IDENTITY, AND THE SPECIFICATION PROVIDES AN ASSAY FOR IDENTIFYING PROTEINS WITN DIPEPTIDYLPEPTIDASE AMIDOLYTIC ACTIVITY

Claims ...63, and 66-75 recite a protein [and variants thereof] having diipeptidylpeptidase amidolytic activity (i.e., function).

Claims ...63, 66-70, and 75 further recite a protein [and variants thereof] having a percentage amino acid identity of greater than 40% (e.g.. claims 58, 63, and 75), 50% (e.g., claims 66), 60% (e.g., claim 67), 70% (e.g., claim 68), 80% (e.g., claim 69), or 90% (e.g., claim 70) with SEQ ID NO: 2 (i.e.. structural identity). Claims 71-75 further recite an isolated nucleic acid comprising a nucleotide sequence having at least about 70% identity (e.g., claims 71 and 75), 80% identity (e.g., claim 72), 90% identity (e.g.. claim 73), or 95% identity (e.g., claim 74), with SEQ ID NO: 1 (i.e.. structural identity). Notably, as described herein above, claim 75 recites structural identity to both a protein and a nucleotide sequence.

The specification describes an assay for identifying proteins having dipeptidylpeptidase amidolytic activity (e.g.. page 12, line 27 to page 13, line 25; page 25, line 22 to page 26, line 2; and page 26, lines 23-32).

Thus, claims ... 63, and 66-75 define a genus through the recitation of both function and structural identity, and the specification provides an assay for identifying dipeptidylpeptidase amidolytic activity. As discussed herein above, Applicants note that the Guidelines state that although only a single species is disclosed the claimed genus meets the written description requirement through recitation of function and structural identity in the claim, and the disclosure of an assay for identifying variants, which are capable of the specified catalytic activity."

Reply: These arguments are not found to be persuasive. It is acknowledged that Claims 63, 66-73, and 75 recite sufficient functional written description. However, the structure of the subject matter of said claims was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It is acknowledged that the specification provides an example of a nucleic acid molecule (SEQ ID NO: 1) that encodes a protein (SEQ ID NO: 2) having dipeptidylpeptidase amidolytic activity. However, the structural elements further recited in Claims 63, 66-73, and 75, as described above, are not sufficient to convey that applicants were in possession of the recited invention. The specification fails to provide examples of nucleic acid molecules, derived from SEQ ID NO: 1 or encoding proteins derived from SEQ ID NO: 2 and having the modifications recited in Claims 63, 66-73, and 75, wherein said examples have dipeptidylpeptidase amidolytic activity. Given this lack of

description of representative species, rejection of Claims 60-73 and 75 under 35 U.S.C. 112, first paragraph for lack of sufficient written description is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

In the Action of July 25, 2003, Claims 39-53 were rejected under 35 U.S.C. 102(a) or (b) over applicant's admission of the prior art. Said rejection is withdrawn because, Claims 39-53 have been cancelled. However, new Claims, 54-56, 58-70, and 77, are hereby rejected for the same reasons described in the prior action.

To support their request for withdrawal of said rejection, Applicants provide the following argument.

"For anticipation to occur, a prior art disclosure must put the public in possession of the invention. Applicants respectfully submit that the sequence designated "P. gingivalis genomic contig gln/TIGR/P. gingivalis 1208," does not contain an enabling disclosure, and thus, did not put the public in possession of the claimed invention.

Independent Claims 54, 60, 63, 71, and 75 each recite "[a]n isolated nucleic acid". The specification recites that "the term 'isolated' means that a polypeptide or a polynucleotide has

been either removed from its native environment, produced using recombinant techniques, or chemically or enzymatically synthesized" (specification at page 6, lines 8-10).

In contrast, the art of the TIGR database disclosed contigs that are part of the P. Gingivalis genome in the Unfinished Microbial Genomes database, and Applicants are not claiming such contigs or the unfinished genome. Moreover, the sequence designated "P. gingivalis genomic contig gln/TIGR/p. gingivalis_1208 provides no guidance as to which sequence of nucleotides might or might not contain an open reading frame. Further, there is no disclosure as to which nucleotide sequence, if any, might encode a protein. Thus, a person of ordinary skill in the art of ordinary skill, having the nucleotide sequence of the genomic clone, would not be able to predict that the open reading frame encoding SEQ ID NO: 1 could be transcribed or translated. Applicants respectfully submit that the disclosure of the unfinished genome is not an enabling disclosure for making the presently claimed isolated nucleic acids (e.g., independent claims 54, 60, 63, 71, and 75), and thus, fails to anticipate claims 54-77.

According to M.P.E.P. 2112 'to establish inherency, the extrinsic evidence must make, clear that the missing descriptive matter is necessarily present in the thing described in the document and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mear fact that a certain thing may result from a given set of circumstances, is not sufficient . . . In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art' M.P.E.P 2112 (emphasis in original).

First Duncan et al, in describing their "shotgun" approach to sequencing state that "[a] random library is best constructed from mechanically sheared fragments since any kind of enzymatic cleavage is generally non-random. [S]heared DNA fragments are blunt-ended, gel fractionated and inserts of average size 1.8-2.5 kb are cloned into pUC18" Duncan et al., page 3. entitled "Constructing Random genomic libraries of P. ginglvalls DNA," second paragraph). Applicants respectfully submit that none of the random 1.8-2.5 kb mechanically sheared DNA fragments disclosed by Duncan et al. necessarily include the entire 2139 nucleotide (2139 kb) sequence, SEQ ID NO: 1. Thus, it is respectfully submitted that the Examiner has not met her burden of providing a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the cited document.

Moreover, even if one of the random mechanically sheared DNA fragments disclosed by Duncan et al arguably did include the entire 2139 nucleotide sequence, SEQ ID NO: 1, there is no teaching or suggestion in Duncan et al to provide guidance as to which random mechanically sheared DNA fragment might or might not contain an open reading frame. Further, there is no disclosure as to which random mechanically sheared DNA fragment, if any, might encode a protein. Thus, a person of ordinary skill, having the random mechanically sheared DNA fragments, would not be able to predict that the open reading frame encoding SEQ ID NO: 1 could be transcribed or translated.

Second, the Examiner is apparently attempting to equate a "contig" (i. e., gln/TIGR/p. gingivalis-1208) disclosed on the Unfinished Microbial Genomes database, TIGR, with one of the random mechanically sheared DNA fragments disclosed by Duncan et al. Appellants

respectfully note that Duncan et al. clearly describe that the assembly of clones results in contigs....

> Assembly of the genome sequence will be performed using TIGR Assembler (Sutton et 2., 1995) which simultaneously clusters and assembles fragments of the genome using a best-match-first strategy. Potentially chimeric fragments and fragments representing the boundaries of repetitive regions are flagged based on partial mismatches at the ends of alignments and excluded from the contig. TIGR Assembler recognizes potentially repetitive regions (those present at more than one copy in the genome) based on 10-mer oligonucleotide frequency. Contig building in repetitive regions is more stringent than in non-repetitive regions to attempt to distinguish among closely related copies of the repeat element. Duncan et al., page 4, under the heading "Assembly").

Thus, Applicants respectfully submit that contigs are not necessarily the same as the random mechanically sheared DNA fragments disclosed by Duncan et al.

Nonetheless, the Examiner alleged that "specific polynucleotide sequences encoding dipeptidylpeptidase and amidolytic activities can be readily identified by analyzing the sequence of the P. Gingivalis TIGR database using commercially available programs such as Prosite" (page 13 of the Office Action mailed July 25, 2003). To the extent that the Examiner is basing the present 35 U-S.C. 102 rejection on an "obvious to try" rationale, Applicants respectfully submit that such a rationale is not appropriate for either an anticipation rejection under 35 U.S.C. 102 or an obviousness rejection under 35 U.S.C. 103.

Thus, Applicants respectfully submit that the Examiner has failed to present a prima facie case for the unpatentability of present claims 54-77 over the sequence designated "P. Gingivalis genomic contig gln/TIGR/P. gingivalis_1208" which the Examiner alleged is admitted prior art by Applicants."

Reply: Regarding rejection of Claims 54-56, 58-70, and 77 under 35 U.S.C. 102(a) or (b, these arguments are not found to be persuasive for the following reasons. It is acknowledged

that the contigs disclosed by TIGR are not necessarily the same as the random mechanically sheared DNA fragments disclosed by Duncan et al. That, more likely than not, the contigs represent sequences derived from computational assembly of the sequences derived from sheared DNA fragments. However, the genomic contig gln/TIGR/p. gingivalis_1208 is a polynucleotide that encodes the protein set forth by SEQ ID NO: 2, as disclosed by Applicants on page 26, lines 11-21:

> "*Identification of the DPP-7 Coding Sequence* -... An identified contig gnl/TIGR/P. gingivalis_1208 was retrieved from the Institute for Genomic Research database. The position of the DPP-7 coding sequence was localized using the National Center for Biotechnology Information (NCBI) open reading frame (ORF) finder and the amino acid sequence, obtained by conceptual translation of the entire ORF, was further used for homology screening by use of the NCBI BLAST search tool."

Thus, by Applicant's admission, the prior art is enabling for the recited invention of any polynucleotide encoding the protein set forth by SEQ ID NO: 2. Furthermore, the sequence of gnl/TIGR/P. gingivalis_1208 would hybridize to SEQ ID NO: 1 under the conditions of Claim 54. One of skill in the art would be able to easily deduce, without additional guidance, those sequences of gnl/TIGR/P. gingivalis_1208 that represent the coding region of the protein set forth by SEQ ID NO: 2.

For these reasons and those described in the prior actions, rejection of Claims 54-56, 58-70, and 77 under 35 U.S.C. 102(a) or (b) over applicant's admission of the prior art is maintained.

Examiner's note: Applicants are reminded of their duty to disclose all prior art relevant the their application. To date, Applicants have not disclosed the sequence, or date of availability to the public, for the genomic contig gln/TIGR/p. gingivalis_1208.

In the Action of July 25, 2003, Claims 39 and 41-53 were rejected under 35 U.S.C. 102(e) as being anticipated by Ross et al, 2002 (filing date Dec 23, 1998). Said rejection is withdrawn, because Claims 39 and 41-53 have been cancelled. However, new Claims 54-56, 58, 63-71, and 75 are hereby rejected under 35 U.S.C. 102(e) as being anticipated by Ross et al, 2002 (filing date Dec 23, 1998). Ross et al teach a polynucleotide having 70.1% identity with SEQ ID NO: 1 wherein said polynucleotide has 99.8% identity with SEQ ID NO: 1 over residues 409-2139. Said polynucleotide encodes a polypeptide having 80.5% identity with SEQ ID NO: 2 wherein said polypeptide has 99.6% identity with residues 137-712 of SEQ ID NO: 2. For the following reasons, it is more likely than not that the polypeptide encoded by the polynucleotide of Ross et al would have dipeptidylpeptidase amidolytic activity. Serine proteases are known to contain a conserved catalytic triad of His/Asp/Ser. For the protein of SEQ ID NO: 2, Ser^{648}, which is found within the protease motif set forth by SEQ ID NO: 25, is the serine of the catalytic triad. A person of ordinary skill in the art would predict that either His^{592} or His^{634} would represent the His within the conserved His/Asp/Ser triad for the protein of SEQ ID NO: 2 and the aspartic acid would lie between one of said histidine residues and Ser^{648}; for example, Asp^{604}, Asp^{617}, or Asp^{642}. The polypeptide encoded by the polynucleotide of Ross et al would be catalytically active as an amidolytic dipeptidylpeptidase, because said polypeptide has 99.6% identity with residues 137-712 of SEQ ID NO: 2 and comprises the His/Asp/Ser catalytic triad of SEQ ID NO: 2 (see sequence alignment from prior actions). Therefore, rejection of Claims 54-56, 58, 63-71, and 75 under 35 U.S.C. 102(e) as being anticipated by Ross et al, 2002 (filing date Dec 23, 1998) is maintained.

To support their request for withdrawal of said rejection, Applicants provide the following arguments.

"Ross et al, in describing their "shotgun approach to sequencing, state that "purified genomic DNA from P. gingivalis was nebulized to fragment the DNA and was treated with Ba131 nuclease to create blunt ends then run twice through preparative 1% agarose gels. DNA fragments of 1.6-2.0 kb were excised from the gel and the DNA recovered" (column 6, lines 44-49. Ross et al. disclose the sequences of 1,120 different DNA fragments (i.e. SEQ ID NO: 1-1120). However, Ross et al. lack a disclosure that any of the 1,120 different DNA fragments encode any protein. Ross et al. also lack a disclosure or suggestion of a protein having dipeptidylpeptidase amidolytic activity.

Moreover, there is no teaching or suggestion in Ross et al. to provide guidance as to which DNA fragments might or might not contain an open reading frame. Further, there is no disclosure as to which DNA fragments if any, might encode a protein. Thus, a person of ordinary skill, having the 1,120 DNA fragments disclose by Ross et al., would not be able to predict that the open reading frame encoding SEQ ID NO: 1 could be transcribed or translated.

...In fact, by pointing specifically to SEQ ID NOs: 176, 192, 214, 243, 273, 417, 524, 638, 758, and 1005 in the claims, Applicants respectfully submit that Ross et al. actually teach away from selecting SEQ ID NO: 726. Moreover, Ross provides no disclosure or suggestion that any of the 1,120 disclosed DNA fragments might encode a protein having the presently claimed dipeptidylpeptidase amidolyic activity. ...

Applicants note that the complete listing for sequence Accession number gi:9968803 on NCBI (Exhibit A) describes the sequence as a "glutamyl endopeptidase." The present

specification recites that "the P. gingivalis DPP-7 displays the consensus sequence characteristic for the catalytic site of the V-8 like proteases, a group of endopeptidase cleaving after glutamic or aspartic acid residues. (page 11, line 18-20; emphasis added). Notably, proteins having dipeptidylpeptidase amidolyic activity, as defined in the present claims, do not cleave the peptide bond between the second and the third amino acids from the N-terminal end of a target polypeptide when tee second amino acid from the N-terminal end ...is a glutamic or aspartic acid residue."

Reply: These arguments are not found to be persuasive for the following reasons. It is not necessary for Ross et al to acknowledge that any of their polynucleotides encode a protein or that any of their polynucleotides encode a protein with dipeptidylpeptidase amidolyic activity. If such characteristics are present, they are inherent to the polynucleotides of Ross et al. A person of ordinary skill in the art would not conclude that because the claims of Ross et al recite SEQ ID NO: 176, 192, 214, 243, 273, 417, 524, 638, 758, and 1005, Ross et al teaches away from SEQ ID NO: 726 because SEQ ID NO: 726 may be prosecuted in a subsequent filing. It is acknowledged that the sequence of Accession #gi:9968803 indicates that said sequence encodes a "glutamyl endopeptidase". Reference to said sequence was not used to argue that the sequence of Ross et al encodes a dipeptidylpeptidase amidolyic activity, but merely that the sequence of Ross encodes a serine protease. The activity of the polypeptide encoded by the polynucleotide of Ross et al as being dipeptidylpeptidase amidolyic activity is inherent to said polypeptide, as discussed above. Therefore, rejection of Claims 54-56, 58, 63-71, and 75 under 35 U.S.C. 102(e) as being anticipated by Ross et al, 2002 (filing date Dec 23, 1998) is maintained.

Allowable Subject Matter

Claims 57, 74, and 76 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan L. Swope, Ph.D.